REMARKS

No amendments have been proposed to the claims and they have been reproduced solely for the convenience of the Examiner.

The Rejection Under 35 U.S.C. § 112, Paragraph 1

All claims were rejected for asserted lack of enablement. This basis for rejection is based solely on the *Wands* factors and applicants respond to the points made by the Office as follows:

First, the Office objects to the breadth of claim 71 and states that it is not supported by the specification. There is no support provided by the Office for this position. Applicants call attention of the Office to the extensive list of biologically active agents beginning on page 18 at line 18 and continuing to page 20, line 21. There is no reason provided by the Office that the invention would not work with any of these drugs, nor is there any reason provided that the application fails to support the breadth of this claim. In any event, the scope of no other claims seems to have been taken account of. For example, claims 95-97, included within this rejection, are quite specific as to the drugs to be employed. Claims 77 and 82 are quite specific with regard to the makeup of the particles. No account appears to have been taken of this.

The Examiner's statement of the nature of the invention is correct, except that it omits an essential feature of the invention which is that the particles must be coupled to a targeting ligand. This is an essential feature because only if the particle is held into contact with the targeted tissue or organ does the prolonged contact of the lipid surfactant layer with the cell membrane exist. It is this prolonged contact that provides the favorable effect of the invention. The statement of the invention

also ignores the requirement for specific types of drugs in claim 71 and the narrowing restrictions of the dependent claims.

As to the state of the prior art, the Office quotes the Kereos website as teaching that drugs containing "hydrophilic payloads" are projected above the ligand-targeted emulsion surfaces. This fails to take account of the particular process required for ensuring that hydrophilic drugs are incorporated into the lipid/surfactant coating as supported by the Declaration of Dr. Gregory Lanza filed herein with the response mailed 27 October 2006.

As Dr. Lanza states in his Declaration, he personally prepared a composition of doxorubicin carrying out the method set forth in the claims and states, in paragraph 3, that doxorubicin, supplied as the hydrochloride, is highly water-soluble and that it is only when it is not incorporated into the solvent film prior to preparation of the particles that it is not incorporated into the lipid surfactant layer. In the application itself, Examples 1 and 2 illustrate the invention, which is as stated on page 7 at line 16, that wherein the biologically active agent is in or on the surface of the outer lipid monolayer of the emulsion and is not carried or deposited in the interior of the emulsion particles.

The Office then purports to quote the website as stating that lipophilic payloads such as many chemotherapeutics are incorporated into the lipid layer and goes on, apparently quoting from the website, stating that not every drug is capable of being "contained in the lipid layer and not carried or deposited in the core." There is no such quote on the Kereos website. This appears to be something that the Office itself has decided on the basis of no evidence at all. The Office goes on to say that "compatible reaction partners" are determined only by experimentation. Applicants do not understand what the Office means by "compatible reaction partners" and are unaware of any "reaction partners" involved in the invention. In any event, there is no basis for this statement.

In the next section, the Office discusses the amount of direction provided by the inventor, stating that there is nothing in the specification that would indicate that the invention works with any and all drug compounds. Again, the Office ignores the specific limitations of the dependent claims, all of which are included in this basis for rejection. The Examiner acknowledges that specific examples are given, but states that the specification somehow fails to teach that this will work with other drugs. No evidence is adduced in support of this statement, and applicants believe there is none.

The Examiner does acknowledge the presence of working examples. In discussing the quantity of experimentation required, the Office concludes that there is a gap that would require undue experimentation to bridge between the exemplification and the scope of the claims. Again, there is no support provided for this position.

The Office does acknowledge that the skill in the art is high.

Reviewing the *Wands* factors, then, the breadth of even the broadest claim is clearly supported by the specification on page 18, lines 21, *et seq.*; and this factor weighs in applicants' favor. The nature of the invention, as it is stated by the Office, seems a neutral factor; the state of the prior art as set forth on Kereos' web page has been characterized as unfavorable, but the web page has been misquoted and the directions in the specification have been ignored; in regard to the amount of direction provided by the inventors, the Office states, without support, that there is inadequate direction rendered by the presence of working examples. The Office at least acknowledges that these are present. With regard to the quantity of experimentation, we have only the unsupported view of the Examiner that much experimentation would be needed, and the relative skill of those in the art is stated to be high. Thus, in the *Wands* factors set forth by the Office, two

of them are favorable to the applicants, by the admission of the Office, and the remainder are either neutral or, with respect to those that are said to be negative, no support has been provided with regard to the negativity.

In the "response to arguments", the Office states that the applicants have not provided evidence why there is no lipophilic drug incorporated into the perfluorocarbon core which is also hydrophobic. This is not true. Applicants have explained that this is assured by performing the required process for ensuring that the drugs are in the lipid/surfactant layer. Please see the response filed 11 December 2007 on page 7. The remaining discussion in response to arguments appears to be directed to what obligations there might be for applicants to distinguish the prior art, and is irrelevant to a rejection based on lack of enablement.

For the foregoing reasons, applicants believe this basis for rejection may, and should be, withdrawn.

The Rejection for Anticipation

All claims were rejected as anticipated by U.S. 5,690,907; U.S. 5,780,010; or U.S. 5,958,371 (in the alternative, as they are substantially identical disclosures) as said to a be evidenced by U.S. 4,595,680; U.S. 5,656,287 or U.S. 6,149,937,

The first point made by the Office is that the particles in the primary documents are coated with lipid/surfactant, are of the sizes required by claims 85-86 and include biotinylated phosphatidyl ethanolamine and cholesterol. The Office persists in arguing that, as evidenced by '680, phosphatidyl ethanolamine is a drug having activity against disorders related to the central nervous system.

First, the Office is invited to read the list of drugs set forth in claim 71 as amended, which does not include any description of even the activity ascribed by the Office to phosphatidyl ethanolamine. Not only has the Office ignored the limitations set forth in claim 71 as to the types of drugs being covered thereby, it has also ignored the arguments previously made by applicants that the disclosure of the entire document of the '680 patent reveals that the only activity it has is an anticoagulant associated with the actual drug that does have activity against disorders related to the central nervous system – *i.e.*, phosphatidylserine (PS). This was set forth extensively on page 8 of the response filed 20 August 2007, for example, for the second time. It had also been agreed at the interview conducted on 19 July 2007 with the Examiner and Supervisor Michael Woodward that this basis for rejection was in error.

In addition, the Office goes on to state that doxorubicin is set forth in the primary documents as a drug that could be included in the nanoparticulate compositions. As the Office itself has noted previously in the Office action, on page 6 thereof, doxorubicin is water soluble, and indeed, doxorubicin is supplied as the hydrochloride which is water soluble. The Office cites the '287 and '937 patents as probative that this water soluble drug would be in the lipid surfactant layer based on the contention that the nanoparticles of the invention are liposomes (which have aqueous cores). Well, if the nanoparticles were liposomes and liposomes have aqueous cores, then a water soluble drug as the Office claims doxorubicin is, would not be expected to be in the lipid layer, but rather would be in the aqueous core with which it is compatible. Having characterized doxorubicin as water soluble, the Office inquires on the same page why paclitaxel, which is hydrophobic, would not go into what the Examiner acknowledges is the hydrophobic core of the present particles. How can the present particles be liposomes and have hydrophobic cores? The Office appears to have

ignored entirely the definitions provided by applicants of liposomes which are clearly different from the nanoparticles of the invention, for example, on page 13 of the response filed 20 August 2007. Applicants do not understand why the Office continues to argue that the nanoparticles of the invention are liposomes. This is especially true since if they were liposomes, one would expect hydrophilic drugs to be in the core, not in the lipid bilayer of these liposomes. In view of this, the '287 and '937 documents are clearly irrelevant.

The Rejection Under 35 U.S.C. § 103

All claims were rejected under this section over the same group of documents that form the basis for anticipation.

The distinction in arguments between those for anticipation and obviousness is not seen. The Office argues that paclitaxel and doxorubicin would automatically reside in the lipid/surfactant layer; applicants have already supplied the Declaration of Dr. Lanza that this is not the case, unless the required procedure is followed. No account appears to have been taken of this. Again, the Office persists in arguing that the nanoparticles of the invention are liposomes, which clearly they are not. This appears to be the basis for the argument by the Office that these compounds would automatically reside in the lipid layer.

As the Office states on page 12, "it would have been obvious … to combine the teachings of '907 with '680, '287 or '937. All teach incorporating drugs into a liposome-type system." They actually do not. The invention systems are not liposome-type systems at all.

In the response to arguments, the Office again ignores the limitation to the types of drugs in the claim in asserting that phosphatidyl ethanolamine is a drug and asserts that '907 discloses the

steps claimed in amended claim 71. It simply does not do that. The '907 provides no discussion of the steps in this claim as including a biologically active agent. There is no description of step (a) of mixing the drugs with the components of the lipid/surfactant layer in a solvent. There are no directions whatsoever given in '907 for ensuring that the drug is in the lipid layer. Respectfully, the Office is reading much more into the '907 disclosure than is there. No example is provided where a drug is actually incorporated into the nanoparticles and no directions are given for any specific manner of incorporating it.

The Office again argues that the nanoparticulate system is a liposome when it clearly is not.

In summary, the Office has provided no fair basis for concluding that the instant claims are anticipated or made obvious by the art.

Conclusion

Applicants point out that the primary documents, while suggesting that drugs may be incorporated into the nanoparticulate emulsions therein described, provide no specific directions for ensuring that that incorporation will be confined to the lipid/surfactant layer. The present application, in contrast, does provide specific instructions for doing so, as the Office itself acknowledges with regard to doxorubicin and paclitaxel (to which claims 96 and 97 are limited). The Office has provided no reason that the methods described in the present case would not be workable with the range of drugs included in the claims and this is verified by Dr. Lanza's Declaration. This Declaration exemplifies both hydrophilic and hydrophobic drugs as adaptable to the method disclosed.

In a somewhat inconsistent manner, the Office argues that the drugs described in the '907 patent would automatically be included in the surface/surfactant layer, a position in direct contrast to the position taken on enablement. Both cannot be true. Applicants have pointed out that it is the method described in the present application that permits this to result and that the description therein is both necessary and adequate to achieve this.

For these reasons, applicants believe that all pending claims herein are in a position for allowance and passage of these claims to issue is respectfully requested.

Should minor issues remain that could be resolved over the phone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532512000401.

Respectfully submitted,

Dated: June 17, 2008 By: / Kate H. Murashige /

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